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REVIEW ARTICLE

Assessment of Acid-Base Disorders

A Practical Approach and Review

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THERE are probably few aspects of medicine that give the average physician as much difficulty as problems associated with disturbances of acid-base balance. In an effort to simplify the analysis of acid-base disorders a number of nomograms have been published but their very number testifies to their apparent lack of success. Adding to the difficulties is the apparent disagreement among even the experts as to the best method for assessing acid-base disorders. Astrup *et al.*[1] have introduced the concept of "standard bicarbonate" and "base excess" as parameters for the measurement of metabolic disturbances of acid-base equilibrium; however, even this simplified approach has been shown to be open to erroneous interpretations.[2]

It seems evident, therefore, that an analysis of acid-base disorders must be based on an understanding of the mechanisms involved in what has been called the "physiological approach"[2] rather than on the uncritical use of some nomogram or formula. Although the following approach to acid-base analysis is neither new nor original, it is hoped that by virtue of its simplicity physicians will be encouraged to become familiar with a group of disorders that are frequently neglected. At the same time, recent developments in the research field will be summarized to provide a clearer understanding of the physiological mechanisms involved. It is the object of this review to relate these developments to clinical practice.

THE PHYSIOLOGY OF ACID-BASE BALANCE

Explanations of the physiological mechanisms of acid-base balance have classically depended upon the derivation of the Henderson-Hasselbalch equation:[3]

$$pH = pK + \log \frac{[HCO_3^-]}{[CO_2]}$$

However, the fact that the equation uses rather complicated computations detracts from its usefulness and tends to obscure relationships between the various parameters. The original version of this equation was proposed by Henderson[4] and was much simpler:

$$[H^+] = K \frac{[H_2CO_3]}{[HCO_3^-]}$$

When equivalent experimentally measurable terms are substituted this formula becomes:

$$\underset{\text{nanoEq./l.}}{[H]^+} = 24 \frac{P_{CO_2}}{[HCO_3^-]}$$

This equation is obviously easier to use than the classical Henderson-Hasselbalch formula, as it does not contain logarithms. Disregarding its derivation, the equation clearly demonstrates that the acidity of the blood or its hydrogen ion concentration ($[H^+]$) is directly related to the partial pressure of carbon dioxide in the plasma (P_{CO_2}) and inversely related to the plasma bicarbonate concentration ($[HCO_3^-]$).

The object of any buffer system such as this is to minimize changes in the $[H^+]$ or the acidity of the blood. Body neutrality may be attacked by a variety of endogenous and exogenous acids but the $[H^+]$ is defended by changes in the P_{CO_2} and in HCO_3^- concentration. The P_{CO_2} is controlled for the most part by pulmonary ventilation, and the plasma bicarbonate level is regulated largely by the kidneys. Thus, when a sudden acid load raises $[H^+]$ and depletes body stores of bicarbonate, the first result is hyperventilation and a reduction in P_{CO_2} (the numerator of the equation) in an attempt to bring $[H^+]$ down. The regeneration of bicarbonate by the kidneys also aids in bringing down the $[H^+]$ by raising the denominator of the equation, although this process is sluggish. Similarly, when the P_{CO_2} rises as a consequence of lung disease, the effect of this on the $[H^+]$ is partly offset by a rise in bicarbonate concentration. It should be noted that although the bicarbonate buffer system is the most important, it is not the only buffer mechanism in the body, as other buffers are found both inside and

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outside the cells. Nevertheless the Henderson equation provides a useful tool for understanding the regulatory mechanisms of a major buffer system and for use in simple calculations.

The term "bicarbonate concentration" has been used, but the term that is commonly used on the wards is "total CO_2". Although "total CO_2" has the advantage of common usage, it is a potential source of confusion because it is a contraction of "total CO_2 content", which refers to the sum of plasma [HCO_3^-] and [H_2CO_3]. It is a term that arose in the laboratory where bicarbonate is measured by converting it to CO_2. However, for practical purposes "total CO_2" and "bicarbonate" can be used interchangeably even though the former contains a small additional fraction of carbonic acid. The "carbon dioxide combining power" is an obsolete method and is not now generally used.

Although the term [H^+] is an expression of acidity that may be unfamiliar to most physicians, it has certain advantages over the equivalent term "pH", which is derived from the logarithm of the reciprocal of the [H^+]

$$\left(\mathrm{pH} = \log \frac{1}{[H^+]}\right)$$

Huckabee[5] has even recommended that the use of the term pH should be abandoned, since it is an artificial derivation not linearly related to [H^+]. However, for the sake of convention, the term pH will be retained although it should be remembered that the direction of change of acidity is reversed; that is, with increased acidity (an increase in hydrogen ion concentration), the pH falls.

LABORATORY TECHNIQUES

(a) *The Blood Sample*

Obtaining the correct sample of blood is the first and probably the most important step in assessing an acid-base problem. If the blood sample is to reflect the acid-base status of the patient, arterial blood is generally used; capillary blood is also suitable, especially if the blood to the area has been "arterialized" by warming the limb. Venous blood is satisfactory for routine analysis provided that it is not taken from a congested or cyanotic area, i.e., a tourniquet should not be used. Venous blood values for total CO_2 content are about 2 to 3 mEq. per litre higher than those of arterial blood and the pH is about 0.02 to 0.04 units lower,[6] so that for more meaningful results arterial blood is preferable.

A committee of the New York Academy of Sciences[6] has recommended the methods to be used in the collection, anticoagulation, storage and separation into its constituents of the blood before the determination of pH and total CO_2 content. Arterial blood is most easily obtained from the femoral, brachial or radial arteries. The area to be punctured is infiltrated with local anesthetic and the blood collected in a syringe, the inside of which has been moistened with heparin. Blood taken in vacuum tubes or capillary tubes is also satisfactory. If the blood is to be centrifuged for the determination of the total CO_2 content of the plasma, it should be kept under oil or in a vacuum tube. Blood can also be centrifuged in the syringe by the use of special holders. Regardless of the method used for separating the plasma, the blood should not be exposed to the air for more than a few minutes and should be analyzed within 20 minutes.

(b) *Analysis*

Before acid-base disorders can be analyzed, blood values for pH, total CO_2 content and P_{CO_2} are required. The measurement of pH is reliable, and with newer models of pH meters, microsamples of blood can be used. By comparison, the determination of the total CO_2 content is more difficult. The original method was developed by Van Slyke and Neill[7] and although the technique is complex, it is still regarded as the standard for other methods. A simple apparatus has been devised by Natelson[8] in which small samples of blood can be used to determine total CO_2 content (probably the most satisfactory piece of equipment for small laboratories). A titration method using the Technicon "AutoAnalyzer" has been developed for large laboratories.[9] For the determination of P_{CO_2}, a direct technique using a glass electrode is now commonly used.* Alternatively the P_{CO_2} can be derived through the use of the "Astrup apparatus" using an interpolation technique, but this has the drawback of needing standard reference gases which should be verified by gasometric analysis in the laboratory where they are being used.[6]

Each laboratory director must obviously choose the method which he finds most suited to his circumstances. Very satisfactory results can be obtained with relatively simple and inexpensive equipment. Usually only the pH and total CO_2 content are measured; the P_{CO_2} is then determined by dividing the total CO_2 content by factors which vary with the pH according to the following formula:

*Radiometer-Copenhagen and Instrumentation Laboratory Inc.

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$$pH = 6.10 + \log \frac{[\text{Total } CO_2] - 0.0301\ P_{CO_2}}{0.0301\ P_{CO_2}}$$

The P_{CO_2} can also be determined from a nomogram (Fig. 1) or pocket calculator (Tri-Slide*). If any two parameters are known, the third can be calculated. The formula that is the basis for these calculations is the Henderson-Hasselbalch equation,[3] but since we have chosen to avoid discussion of this equation, it is sufficient to take the formula and nomograms at face value. A rapid method for the estimation of P_{CO_2} from the pH and total CO_2 content has been devised, using a simple mental calculation that obviates the need for tables or nomograms.[10] The first step is to convert pH to hydrogen ion concentration($[H^+]$) and this is estimated, in nanomoles per litre, from the two digits following the decimal point of the pH value. This number and the value for the total CO_2 content are inserted in the Henderson equation (see above), which is solved for the P_{CO_2}.

ANALYSIS OF THE ACID-BASE DISORDER

When the pH, total CO_2 content and P_{CO_2} have been determined, an analysis of some of the more common acid-base disorders is possible. It is recognized that a complete assessment cannot be made without information about the patient's clinical condition as well as the values for hemoglobin concentration, P_{CO_2}, sodium, chloride and potassium levels in the serum and the degree of oxygen saturation. However, since the scope of this review is limited, only the analyses of the major acid-base parameters will be considered.

Certain generalizations have already been alluded to, viz., that the P_{CO_2} is primarily under control of the lungs and the bicarbonate is controlled primarily by the kidneys. The normal value for P_{CO_2} is approximately 40 mm. Hg and the normal level of bicarbonate is approximately 25 mEq. per litre. Compensatory changes occur in response to primary changes in either the P_{CO_2} or the bicarbonate level, and even though the compensation is never sufficiently complete to bring the pH back to normal, the effect is to minimize the change in pH. (Some of the most rewarding research has arisen from studies of this compensatory process.)

Discussion will be limited to the primary or "pure" disorders: (1) metabolic acidosis, (2) metabolic alkalosis, (3) respiratory alkalosis, (4) respiratory acidosis and (5) one of the common mixed disturbances. Some rules-of-thumb will be supplied to aid the physician in obtaining a practical and rapid analysis of the acid-base disturbance. (For a more detailed presentation the reader is referred to the excellent reviews already available.[11])

*Baxter Laboratories Inc.

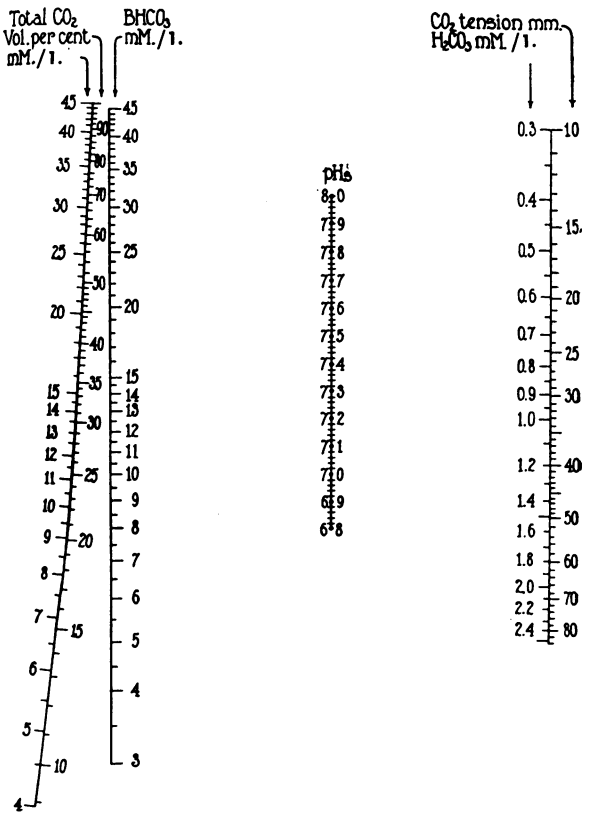

Fig. 1.—Alignment nomogram for obtaining the P_{CO_2} from the total CO_2 content and the pH of the blood.[30] (Reproduced by permission of the *Journal of Biological Chemistry*.) A straight line extended from values plotted on the total CO_2 and the pH scale will intersect the CO_2 tension scale and give the unknown P_{CO_2}.

1. METABOLIC ACIDOSIS

The primary acid-base changes in this disorder are reductions in the plasma bicarbonate concentration and in pH. The P_{CO_2} also decreases as the result of compensatory hyperventilation which tends to minimize the fall in pH. Cases of metabolic acidosis may be divided into two groups, those with a *normal* "anion gap" (10 to 12 mEq. per litre) and those with an *abnormally large* "anion gap". (The anion gap is defined as the difference between (1) the serum sodium concentration and (2) the sum of the plasma bicarbonate and serum chloride concentrations. This gap is normally made up of anions, such as phosphate, sulfate and organic anions, and the anionic groups of plasma proteins that are not usually measured.)

Metabolic acidosis with a normal anion gap occurs when there is a fall in bicarbonate concentration accompanied by a proportionate in-

crease in chloride concentration. This occurs: (1) when bicarbonate is lost from the body in equal amounts with sodium, as in diarrhea or with pancreatic fistula or (2) when hydrochloric acid is effectively added, either exogenously by ingestion of ammonium chloride or endogenously through deficient hydrogen ion excretion as in renal tubular acidosis.

An abnormally large anion gap indicates that the metabolic acidosis is due to accumulation of acids not normally found in significant quantities in the body—ketoacids, lactic acid, salicylic acid, etc. It is also found in uremia, in which case there is excessive accumulation of phosphate and sulfate, but this does not mean that these anions are the cause of the acidosis.

With the onset of metabolic acidosis a certain amount of respiratory compensation occurs in the form of hyperventilation. Obviously if there is lung disease there will be less capacity to hyperventilate and the decrease in pH will be more severe. It therefore becomes important to know what decrease in P_{CO_2} can be normally expected for a given degree of pure metabolic acidosis. This problem has been clarified by Lennon and Lemann,[12] who studied subjects who had been given large doses of ammonium chloride and subjects with acidosis due to chronic renal failure. It was found that the decrease in P_{CO_2} was roughly proportional to the decrease in bicarbonate concentration: with a bicarbonate level of 15 mEq. per litre (i.e. a reduction of 10 mEq. per litre), the P_{CO_2} should be about 30 mm. Hg, a reduction of 10 mm. Hg. This rule-of-thumb relationship between bicarbonate concentration and P_{CO_2} is only approximate; Fig. 2 shows the normal ranges more exactly. When the P_{CO_2} is not within the expected range for a given level of bicarbonate concentration, a superimposed respiratory acid-base disturbance is present.

Even though details of the causes and treatment of metabolic acidosis can be found in any standard textbook of medicine, a few therapeutic hints are included. The advantages of bicarbonate over lactate therapy have been persuasively presented,[13] but, in any case, care must be taken not to overload the cardiovascular system with large quantities of sodium. If sodium bicarbonate is to be given, it is best diluted so as to make an isotonic solution; this is most easily done by adding three ampoules of 50 ml. (3.75 g. or 44.6 mEq. each) of $NaHCO_3$ to a litre of 5% dextrose in water. Minor degrees of metabolic acidosis, i.e. bicarbonate concentrations not below 18 mEq. per litre, are probably best left untreated. The level of hyperventilation is a poor guide to the results of treatment since over-breathing may continue for some time after the patient has been treated with alkali and is no longer severely acidotic.[14]

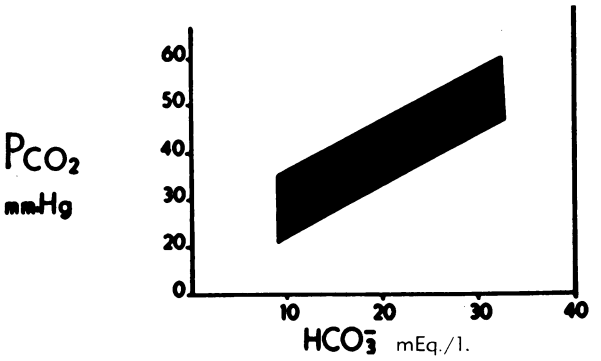

Fig. 2.—Significance band for venous P_{CO_2} in metabolic acidosis.[12] Values falling within the band will, with 95% probability, indicate an uncomplicated metabolic acidosis. (Reproduced by permission of the *Annals of Internal Medicine.*)

2. METABOLIC ALKALOSIS

Although metabolic alkalosis may be a sign of adrenocortical overactivity, steroid therapy, chronic vomiting or excessively vigorous diuretic therapy, the alkalosis itself produces few symptoms. The primary importance of this disturbance lies in the insight that it provides into the physiological mechanisms of acid-base disorders.

The primary blood changes that exist in metabolic alkalosis are an increased bicarbonate concentration and pH. Compensatory hypoventilation may cause a slight rise in P_{CO_2}. The development of the alkalosis is usually due to excessive loss of hydrogen ions either from the stomach or the kidney. Potassium depletion was formerly considered an important mechanism in the etiology of metabolic alkalosis and it was thought to be due to the migration of hydrogen ions from the extracellular fluid into cells in exchange for potassium ions, which left the extracellular fluid alkaline. Although this may be one mechanism, a more important factor in the pathogenesis of the alkalosis seems to be chloride depletion. Chloride and potassium depletion can be induced in a number of ways, e.g. by desoxycorticosterone administration[15] or by diuretic therapy.[16] Chloride deficiency alone and hypochloremia can also be induced by nitrate infusion[17] or by gastric suction.[18] Regardless of the method of induction of the alkalosis, one fact is important: chloride has to be supplied before the alkalosis can be completely corrected regardless of whether or not the potassium depletion was corrected first.[15, 18, 19] Another important experimental finding was the discovery of

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the relationship of potassium to chloride depletion; excessive urinary loss of potassium and potassium deficiency occur when chloride depletion is caused by gastric suction even when gastric losses of potassium, sodium and water are replaced.[18] This potassium deficit is resistant to a normal potassium intake and can only be corrected when chloride is also provided.

The following explanation of the role of chloride in acid-base metabolism has been proposed by Schwartz and his colleagues.[15, 20] Normally, sodium that is filtered at the renal glomerulus is virtually completely reabsorbed during its passage along the renal tubule. In order to preserve electrical balance, however, it cannot be reabsorbed alone but must be either accompanied by an anion such as chloride or exchanged for another cation such as potassium or hydrogen ion. Usually chloride accompanies the sodium, but when there is a deficiency of chloride due to chloride depletion, then exchange for the cation potassium or hydrogen increases. When hydrogen ion is excreted into the renal tubule in this manner, the effective result is the regeneration of a bicarbonate ion and when this process becomes greatly accelerated the plasma bicarbonate level in the blood may increase above normal. Although metabolic alkalosis develops, the loss of valuable quantities of sodium with resultant volume-depletion is avoided. The excessive hydrogen ion and potassium ion loss can be halted by supplying adequate amounts of chloride. More chloride is then filtered at the glomerulus and made available for reabsorption with sodium from the renal tubular lumen. This makes the increased hydrogen and potassium excretion unnecessary, with the result that the renal threshold for bicarbonate falls and the alkalosis is repaired. Therefore it is concluded that the anion chloride plays a much more important role in acid-base and potassium metabolism than was appreciated formerly. There is some recent evidence that suggests that expansion of extracellular fluid volume may also contribute to the correction of the alkalosis by diminishing sodium reabsorption through the so-called "third factor" effect.[21]

The above experimental findings have several important clinical implications. If metabolic alkalosis associated with potassium deficiency is to be prevented or treated, it is necessary to provide potassium in the form of potassium chloride rather than as potassium lactate, carbonate or bicarbonate. Since oral forms of potassium chloride may cause gastrointestinal ulceration, intravenous administration is preferable. In cases of vomiting or prolonged diuretic therapy, it is important to remember that potassium depletion may occur as a consequence of chloride loss alone, even though adequate amounts of potassium are being supplied. Complete potassium repletion will not occur until chloride is given as well. This can be pertinent in cases of digitalis intoxication.

3. Respiratory Alkalosis

Although this is a common condition, because it is the result of hyperventilation, it is not of serious clinical significance even when tetany is present. Over-breathing results in a fall in P_{CO_2}, with a consequent rise in pH. There may be some fall in the bicarbonate concentration, but the chief importance of this acid-base disturbance is in the fact that it may complicate the analysis of other acid-base disorders. Little is known about the long-term effect of chronic respiratory alkalosis, since it is difficult to reproduce experimentally.

4. Respiratory Acidosis

Clinically this disturbance usually occurs in association with chronic lung disease. The primary acid-base abnormality is retention of carbon dioxide, that is, an increase in P_{CO_2}. This hypercapnia is accompanied by a fall in blood pH which is partly offset by a compensatory rise in plasma bicarbonate concentration.

During the first few hours after the onset of carbon dioxide retention, minor compensatory changes occur through the generation of bicarbonate from titration of body buffers. The resulting increase in plasma bicarbonate concentration is slight, however, and insufficient to protect the blood pH against acute increases in carbon dioxide tension;[22] only after the hypercapnia has been present for several days does significant compensation occur. This secondary or chronic response is brought about by the increased reabsorption of bicarbonate by the kidneys which results in a progressive increase in plasma bicarbonate concentration over several days to levels which depend upon the degree of hypercapnia. Although the compensatory response is not enough to bring the pH to normal, it would obviously be very useful clinically to know to what degree the body, by increasing plasma bicarbonate levels, would respond to chronic elevations of CO_2 tension. In other words, what is the normal compensatory response in cases of pure chronic respiratory acidosis? This has been defined experimentally with animals studied in a special chamber at various increased levels of CO_2 tension in which five days or more were allowed for full compensation.[23]

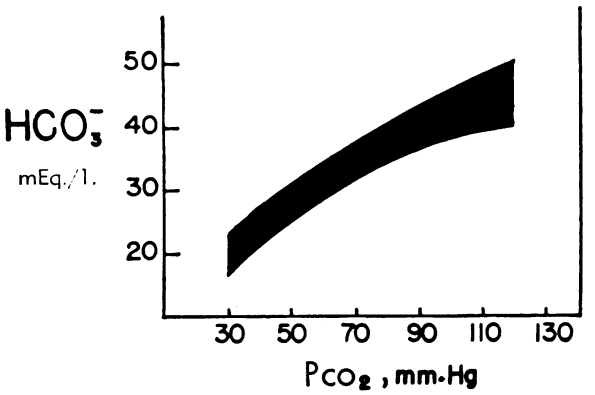

Fig. 3.—Significance band for bicarbonate concentrations in chronic hypercapnia.[23] Values falling within the band will, with 95% probability, indicate an uncomplicated chronic respiratory acidosis. (Reproduced by permission of the *Journal of Clinical Investigation.*)

The degree of adaptation that occurs "normally" with uncomplicated carbon dioxide retention of various degrees is demonstrated in Fig. 3. The result is a "whole-body" carbon dioxide titration curve, and the limits of the band outline the normal ranges. With this curve the clinician has a tool for the analysis of chronic respiratory acidosis. If a bicarbonate concentration is outside the ranges of the confidence bands for a given level of P_{CO_2}, the chances are that there is a superimposed metabolic acid-base disturbance. In the absence of the curve, the following rule-of-thumb can be used: for every 3 mm.Hg rise in P_{CO_2} the bicarbonate concentration can be expected to go up by 1 mEq. per litre. (For further details of this analysis the editorial by Cohen and Schwartz[24] should be consulted.)

Although the above chronic experimental conditions cannot be duplicated in humans, there is considerable evidence that the same whole-body CO_2 titration curve applies. Studies of a large series of men with various degrees of chronic lung disease and hypercapnia revealed a "carbon dioxide response curve"[25] that was very similar to the data shown in Fig. 3. For clinical purposes, therefore, the above guidelines can be used to distinguish a "normal" adaptive response in chronic hypercapnia from that of respiratory acidosis complicated by metabolic acid-base abnormalities.

The mechanism whereby the generation of bicarbonate is increased with hypercapnia has also been clarified.[26] Suffice it to say that the cause is thought to be a combination of tissue buffers and accelerated hydrogen ion excretion resulting in increased bicarbonate reabsorption. The details of the mechanism are not known, but some loss of chloride does occur during the adaptive period. Whether this rejection of chloride by the kidney is a primary or secondary effect has not been determined.

It has also been pointed out that the plasma level of bicarbonate may remain elevated even though the lung disease and hypercapnia which initially caused the respiratory acidosis have improved. This "post-hypercapnic alkalosis"[27] indicates that too little chloride was given to the patient during the recovery phase, with the result that the renal threshold for bicarbonate remained high. It can be corrected by liberalizing the salt-free diet or by giving chloride in some form.

5. MIXED ACID-BASE DISORDERS

Several combinations of respiratory and metabolic acidosis and alkalosis can exist, but with the help of the above-mentioned data the presence or absence of an additional acid-base problem can usually be determined.

Particular mention should be made of the most common mixed acid-base disturbance—metabolic alkalosis superimposed on respiratory acidosis. This is often a complication of cor pulmonale and is due to an inordinate elevation of plasma bicarbonate concentration brought about by salt restriction and diuretics.[28] Thus the therapy for the cardiac problem may complicate the respiratory acidosis. The importance of this excessive "compensation" is that it may aggravate the symptoms of respiratory acidosis by raising P_{CO_2} and pH and decreasing respiratory drive. The superimposed metabolic alkalosis can be treated by giving potassium chloride, arginine hydrochloride or ammonium chloride, the latter being the least desirable. Sodium chloride usually is not given in order to avoid cardiac overload, although, as explained previously, almost any other chloride compound would be expected to have the desired effect. The result should be a slight fall in bicarbonate concentration and P_{CO_2} to levels expected in pure chronic respiratory acidosis. More important is that an associated clinical improvement has sometimes been noted when the superimposed alkalosis was treated.[29]

Summary There have been many attempts to simplify the analysis of acid-base disturbances, but most have depended upon the uncritical use of some new nomogram, formula or artificially derived variable. The present approach relies instead upon the interpretation of changes in the three classic parameters, pH, bicarbonate and P_{CO_2}, augmented by a thorough understanding of the physiological mechanisms which control them. The physiological relationships between these parameters are expressed most simply by the Henderson

equation which, together with a brief discussion of laboratory techniques, forms the background for the analysis of acid-base disorders. Four major acid-base disturbances are discussed, metabolic acidosis, metabolic alkalosis, respiratory alkalosis and respiratory acidosis, as well as one common mixed disturbance—metabolic alkalosis superimposed on respiratory acidosis. Normal compensatory changes that occur in response to the primary acid-base alterations are emphasized, and reviewed experimental work indicates the degree of compensation that is likely to occur in a given pure or uncomplicated acid-base alteration. A review of the recent pertinent experimental literature provides physiological explanations which make the analysis of acid-base disorders more understandable.

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